IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

	Antonio Cosme Gomez	:	Examiner:	S.A. Reynolds
Serial No.:	10/558,801	:	Art Unit:	1623
Filed:	July 14, 2003	:	Confirmation No.:	6905

For: ADDITION SALTS OF AZITHROMYCIN AND CITRIC ACID AND PROCESS FOR PREPARING THEM

DECLARATION OF ANTONIO COSME GOMEZ

1. I, Antonio Cosme Gomez, hereby declare and say:

2. I am one of the inventors of the invention set forth in the above application.

3. I am employed at QUIMICA SINTETICA, S.A. of Barcelona, Spain and am an expert in the field of organic chemistry, the synthesis of organic compounds and in techniques used to characterize them.

4. I received a Ph.D. in Organic Chemistry from the University of Alcala de Henares in Madrid, Spain.

5. I am familiar with the prosecution history of the above-identified application, U.S. Patent Application No. 10/558,801, including an Office Action dated October 29, 2007 as well as the references cited therein, including Asero et al., U.S. Patent No. 6,277,829 ("Asero") and Khamar et al., PCT Publication No. WO 02/07736 A1 ("Khamar").

6. I declare that I am the author of the attached research and development report prepared for Quimica Sintetica, S.A, dated June 23, 2003, entitled "Stability Study of Azithromycin Monohydrate, Citrate, and Hidrogencitrate."

7. In the October 29, 2007 Office Action, claims in the above application, have been rejected as unpatentable over Asero and Khamar. The Examiner has combined these two references to support his position that our invention is obvious. In particular, he has indicated that Khamar and Asero disclose combining citric acid and azithromycin, but do not disclose isolation of azithromycin hydrogen citrate by crystallization. The Examiner maintains, however, that since crystalline azithromycin is well known in the art, such as azithromycin dehydrate, a person of ordinary skill in the art would have been motivated to make the crystalline salt of azithromycin because the salt would have been expected to possess similar properties as known crystalline forms of azithromycin.

8. The Examiner maintained that in Applicants' reply of September 14, 2007, Applicants did not present any evidence that azithromycin hydrogen citrate is not present in the compositions disclosed by the prior art.

9. Asero discloses a process for preparing an aqueous formulation for ophthalmic use containing azithromycin. According to Asero, the solution containing azithromycin, acid citric and the acceptable polybasic phosphate must be adjusted to a value of 5.5–7.6 (see column 3, lines 44-58) in order to achieve an stable aqueous formulation. In particular, in Figure 3 it is indicated that formulations of the invention are stable at pH 6.4/8.7. Asero also seeks an antimicrobial ophthalmic formulation and discloses (see Col. 10, last paragraph) that ophthalmic solutions are affected from pH, so it should be selected an appropriate pH range wherein the ophthalmic solutions still be effective to inhibit the activity of azithromycin against the most important pathogens causing ocular infections; see Example 5 of "In vitro antibacterial activity," wherein the

azithromycin solutions were at pH 6.5, 7.2, 7.8. Therefore, the step of adjusting pH to the range from 5.5 to 7.6 is an essential feature in the process described by Asero.

10. Khamar is directed to providing a clear liquid pharmaceutical composition of azithromycin and discloses that (see "Summary of the Invention" section on page 3, second paragraph) the method for preparing clear liquid pharmaceutical composition of azithromycin is made possible by solubilizing azithromycin in water at pH 4.0 to 6.0 and then adding sodium hydroxide, thereby changing the pH between 6.0 to 7.0. In the method of Khamar, the pH value of the solution, in this case containing only azithromycin, is adjusted to a higher pH value, between 5.5 to 7.0, in order to achieve an azithromycin liquid composition stable for longer period (see page 3, third paragraph). In particular, Khamar states that when a solution is prepared using azithromycin at pH between 4.0 to 6.0, it does not remain stable for a long term and thus, the pharmaceutical composition is not stable.

11. The attached study shows that the azithromycin hydrogen citrate salt of the subject application could not be made by the processes taught by Asero and Khamar which both require the alteration of pH. The references further state that the salt of the invention is not stable. The study shows that no modification of pH was made to attain the azithromycin hydrogen citrate salt of the invention and that the salt is stable.

12. As shown in the attached document and the table below, no alteration of pH was made to attain the azithromycin hydrogen citrate of the invention, yet the azithromycin hydrogen citrate of the invention remained stable over a course of time.

13. We prepared several batches of azithromycin monohydrate at different scales and we studied the stability of the monohydrate crystalline form as a function of time using spectrometric techniques including as Infrared Spectroscopy and Nuclear Magnetic Resonance.

14. To study the impurity profile of azithromycin monohydrate at room temperature, we carried out an HPLC purity study.

15. The results of the study set forth in the attached document and the table below, clearly show that the impurity level increased with time.

Table 1. Azithromycin monohydrate stability results.

Azithromyzin	Storage time at RT	%Azithromicin	%Imp Tr 3.0 min	%Imp Tr 5.0 min	%Imp Tr 5.3 min	%Imp Tr 7.2 min	%Imp Tr 8.2 min	%Imp Tr 16.4 min	Total impurities (%)
03RT028	t = 0	98.88	0.28	0.04	0.03	0.02	0.03	0.09	1.12
03RT029	t = 0	98.84	0.03	0.09	0.07	0.09	0.10	0.04	1.16
03RT030	t = 0	97.97	0.05	0.23	0.22	0.28	0.32	0.25	2.03
03RT031	t = 0	97.46	0.79	0.19	0.16	0.19	0.21	0.25	2.54
03RT040*	t = 0	---	--	--	--	--	--	--	--
03RT028	45 days	95.28	0.11	0.84	0.48	0.87	0.53	0.85	4.72
03RT029	45 days	95.39	0.10	0.65	0.55	0.82	0.48	0.74	4.61
03RT030	45 days	94.19	0.17	1.06	0.62	1.15	0.56	0.98	5.81
03RT031	45 days	96.01	0.82	0.93	0.09	0.69	0.21	0.50	3.99
03RT040	45 days	96.01	ND	0.55	0.31	0.91	0.66	0.48	3.99

*This compound was no analyzed initially

16. Further tests were carried out to study the stability of azithromycin citrate and hydrogencitrate prepared in the laboratory.

17. The stability studies were carried out at both room temperature and at 80°C. The results of the study, as shown in the table below, indicate that both azithromycin citrate and hydrogencitrate are very stable at room temperature, but only the hydrogencitrate is stable at 80°C.

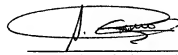
Table 2. Azithromycin citrate and hydrogencitrate stability results.

Azithromyzin	Time storage (days)	T° storage	KF (%)	pH (10% in water)	HPLC purity (% areas)	% major impurity	Total impurities
03RT065	t = 0	RT	7.0	6.92	98.91	0.24% at Tr = 4.3 min. 0.17% at TR = 5.4 min. 0.16% at Tr = 22.9 min	1.09%
03RT066	t = 0	RT	5.02	4.95	99.62	0.09% at Tr = 4.3 min. 0.14%at TR = 22.9 min.	0.38%
03RT067	t = 0	RT	3.42	5.15	99.15	0.23% at Tr = 1.36 min. 0.16% at TR = 4.3 min.	0.85%
03RT065	30	RT	7.77	7.14	99.57	0.09% at Tr = 4.8 min.	0.43%
03RT066	30	RT	5.15	5.14	99.80	0.06% at TR = 22.3 min.	0.20%
03RT067	30	RT	4.34	5.13	99.95	0.01 % at Tr = 4.6 min. 0.02% at TR = 27.2 min.	0.05
03RT065	17	80°C	6.82	6.74	81.29	5.88% at Tr=1.39min. 11.18% at TR = 5.99min.	18.71%
03RT067	17	80°C	4.06	5.16	98.74	0.61% at Tr = 4.66 min.	1.26%

18. In our testing, we attained the azithromycin citrate and hydrogen citrate without alteration of pH. The azithromycin citrate and hydrogencitrate prepared were very stable at room temperature.

I hereby declare that all statements made herein of my own knowledge are true, that all statements mode on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

January 28, 2008



Antonio Cosme Gomez

STABILITY STUDY OF AZITHROMYCIN MONOHYDRATE

Stability study of the monohydrate crystalline form

We have prepared several batches of azithromycin monohydrate at different scale and studied the stability of the monohydrate crystalline form with the time.

When we have worked in a small scale (we have prepared four batches of 0.15 Kg/batch at laboratory (ref. 03RT028-31) and one of 0.84 Kg/batch at pilot plant (ref. 03RT040) of the monohydrate form), the batches obtained kept the monohydrate crystalline form during at least 2 months.

However, when a higher batch (12 Kg/batch; ref. RH03005) of the monohydrate form was obtained in the pilot plant, the crystalline form was no stable, being transformed from the monohydrate form to the dihydrate form with the time or even in the drying shed during the drying step.

Note: the analysis of the crystalline forms were carried out using spectrometric techniques (IR and ^{13}C NMR).

Impurity profile study of the Azithromycin monohydrate form at rt.

We have carried out the HPLC purity study of the above Azithromycin batches with the time.

The results of this study are colleted in the following table, showing that the impurities level increase with the time to give products out of specifications.

Table 1. Azthromycin monohydrate stability results.

Azithromyzin	Storage time at RT	%Azithromicin	%Imp Tr 3.0 min	%Imp Tr 5.0 min	%Imp Tr 5.3 min	%Imp Tr 7.2 min	%Imp Tr 8.2 min	%Imp Tr 16.4 min	Total impurities (%)
03RT028	t = 0	98.88	0.28	0.04	0.03	0.02	0.03	0.09	1.12
03RT029	t = 0	98.84	0.03	0.09	0.07	0.09	0.10	0.04	1.16
03RT030	t = 0	97.97	0.05	0.23	0.22	0.28	0.32	0.25	2.03
03RT031	t = 0	97.46	0.79	0.19	0.16	0.19	0.21	0.25	2.54
03RT040*	t = 0	--	--	--	--	--	--	--	--
03RT028	45 days	95.28	0.11	0.84	0.48	0.87	0.53	0.85	4.72
03RT029	45 days	95.39	0.10	0.65	0.55	0.82	0.48	0.74	4.61
03RT030	45 days	94.19	0.17	1.06	0.62	1.15	0.56	0.98	5.81
03RT031	45 days	96.01	0.82	0.93	0.09	0.69	0.21	0.50	3.99
03RT040	45 days	96.01	ND	0.55	0.31	0.91	0.66	0.48	3.99

*This compound was no analyzed initially

AZITHROMYCIN CITRATE AND HIDROGENCITRATE STABILITY AT RT AND 80°C.

We have also studied the stability of Azithromycin citrate (ref. 03RT065) and hidrogencitrate (ref. 03RT066 and 03RT067) prepared at the laboratory.

The stability studies have been carried out at rt and 80 °C and the results of this study are collected in the table 2. As we can see, both compounds are very stable at rt, however, only the hemicitrate is stable at 80 °C where the citrate have shown to be very instable.

Table 2. Azithromycin citrate and hidrogencitrate stability results.

Azithromyzin	Time storage (days)	T° storage	KF (%)	pH (10% in water)	HPLC purity (% areas)	% major impurity	Total impurities
03RT065	t = 0	RT	7.0	6.92	98.91	0.24% at Tr = 4.3 min. 0.17% at TR = 5.4 min. 0.16% at Tr = 22.9 min	1.09%
03RT066	t = 0	RT	5.02	4.95	99.62	0.09% at Tr = 4.3 min. 0.14%at TR = 22.9 min.	0.38%
03RT067	t = 0	RT	3.42	5.15	99.15	0.23% at Tr = 1.36 min. 0.16% at TR = 4.3 min.	0.85%
03RT065	30	RT	7.77	7.14	99.57	0.09% at Tr = 4.8 min.	0.43%
03RT066	30	RT	5.15	5.14	99.80	0.06% at TR = 22.3 min.	0.20%
03RT067	30	RT	4.34	5.13	99.95	0.01 % at Tr = 4.6 min. 0.02% at TR = 27.2 min.	0.05
03RT065	17	80°C	6.82	6.74	81.29	5.88% at Tr=1.39min. 11.18% at TR = 5.99min.	18.71%
03RT067	17	80°C	4.06	5.16	98.74	0.61% at Tr = 4.66 min.	1.26%

CONCLUSIONS

1.-The azithromycin monohydrate is not estable because:

a.-The crystalline form of the azithromycin monohydrate was not stable with the time during the scale up.

b.-The impurities level of the azithromycin monohydrate increase with the time to give products out of specifications.

2.-The azithromycin citrate and hidrogencitrate are very stable at rt.

3.-The azithromycin hidrogencitrate is more stable that the azithromycin citrate.